Polymorphisms of candidate genes, associated with the risk of pre-eclampsia

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INTRODUCTION

Pre-eclampsia (PE) - is a complication of pregnancy, characterized by arterial hypertension, proteinuria, edema, as well as by deep disorders of the vascular system, hemostasis, immunity, hemodynamics and microcirculation, fetoplacental insufficiency, kidney, hepatic, and lungs malfunctions.[1,2]

The prevalence of PE is 4–18% among all pregnant women,[3] and the perinatal mortality rate is 23–27%.[4]

An important role in the etiology and pathogenesis of PE belongs to the folate candidate genes.[5-7] Mutations in the genes of folate metabolism, causing the decrease in the activity of enzymes of methyltetrahydrofolate reductase and methionine synthase reductase, lead to accumulation of homocysteine in the body of a pregnant woman, and to a deficiency of folic acid.[5,6] Deficiency of folic acid affects the proliferation of chorionic cells and the formation of placenta. This complicates the course of gestation, increasing the risk of placental insufficiency, PE and other disorders of prenatal development. The role of candidate genes of folate metabolism in the formation of PE is actively studied, but these studies often give conflicting results for different populations.[5,6,8-12]

MATERIALS AND METHODS

Object of Study

The study group included 274 pregnant women, diagnosed with PE, and 179 women with normal gestation course. The study group included 247 pregnant women, without hereditary burden, high frequencies of alleles +2756G MTR (odds ratio [OR] = 1.61, P = 0.01) and the genotype +2756GG MTR (OR = 7.26, P = 0.0007, p bonf = 0.0021) were revealed. Conclusions: Thus, as a result of this study, significant associations of polymorphism of the methionine synthase gene +2756A>G MTR with the risk of PE were established, depending on the burdened familial history.

KEY WORDS: Genetic polymorphism, Folate cycle genes, Pre-eclampsia, Pregnancy
Molecular and Genetic Methods

Typing of the following polymorphic variants of folate cycle genes was carried out for all pregnant women with PE and pregnant women from the control group methylene tetrahydrofolate reductase (+677C>T MTHFR [rs1801133] and +1298A>C MTHFR [rs1801131]), methionine synthase reductase (+66A>G MTRR [rs1801394]), methionine synthase (+2756A>G MTR [rs1805087]), thymidylate synthetase (−1053C>T TYMS [rs699517], IVS6-68 C>TTYMS [rs1059394], and −1122A>G TYMS [rs2790]). All polymorphic variants of folate cycle enzymes were analyzed using the method of polymerase chain reaction (PCR) of DNA synthesis in real-time (real-time-PCR).

Statistical Methods

Gene and phenotypic frequencies were calculated using the standard methods. The conformity of the observed distribution of genotypes to the expected one, according to the Hardy-Weinberg equilibrium, was performed using the χ² criterion. The Bonferroni correction was used when carrying out multiple comparisons.

The associations of alleles and genotypes of the studied polymorphic variants with the formation of PE were assessed using 2 × 2 conjugation tables, with the calculation of χ² criterion, with the Yates correction for continuity and odds ratio (OR), with 95% confidence interval.[14]

RESULTS

Significant differences were not revealed in the process of comparative analysis of the frequency distribution of alleles and genotypes of polymorphic markers of folate cycle genes in the group of pregnant women with PE, having hereditary burden, and in the group of healthy pregnant women (taking into account the Bonferroni correction).[15,16]

In the group of pregnant women with PE, without hereditary burden, high frequencies of alleles +2756G MTR (33.73%), IVS6-68T TYMS (29.01%), and the genotype +2756GG MTR (15.53%) were found, in comparison with the pregnant women from the control group (21.30%, OR = 1.61; 95% CI = 1.12–2.31; χ² = 6.87; P = 0.01; 21.50%, OR = 1.49; 95% CI = 1.02–2.18; χ² = 4.31; P = 0.04; 2.47%, OR = 7.26; 95% CI = 2.32–25.29; χ² = 15.29; P = 0.0007; bonf = 0.0021).

When using Bonferroni correction, the differences between pregnant women with PE, without a burdened familial history, and pregnant women from the control group were statistically not significant for the genotype IVS6-68TT TYMS.[17]

DISCUSSION

The results of this study show that polymorphism of the methionine synthase gene +2756A>G MTR has significant pathogenetic importance for the occurrence of PE. The allele +2756G MTR and the genotype +2756GG MTR are associated with a risk of PE in pregnant women without a burdened familial history.

Methionine synthase (MTR) is one of the most important enzymes of folate metabolism. This cytoplasmic enzyme catalyzes the reaction of homocysteine methylation, with its conversion to methionine, using 5-methyltetrahydrofolate as a donor of the methyl group, thereby reducing the concentration of homocysteine in blood. The polymorphism of the gene +2756A>G MTR is associated with the replacement of asparagine to glycine at the 919 position of the protein, that may affect its secondary structure, and therefore has a functional significance.[19]

In other studies on the search for the associations of folate cycle genes with the risk of PE, opposite results were obtained. Thus, in the studies on the Polish, Spanish, and South American populations, there was no association of polymorphism of gene +2756A>G MTR with the risk of PE development.[19]

The inconsistency of the results, obtained in various studies, may be related to the differences in the ethnic and, respectively, genetic background of the studied populations. Even the population of certain regional groups of Russians (Belgorod region, the south of Central Russia, the center of Central Russia) is so genetically diverse, as some of the nations of Western Europe (Germans, Norwegians, etc.) and is significantly higher than the variability of most ethnic Slavic groups (Bulgarians, Czechs, Poles).[20,21] This feature of the Russian gene pool determines the need to take into account the population sample, for which the results are obtained.

SUMMARY

Thus, as a result of this study, significant associations of polymorphism of the gene +2756A>G MTR with the risk of PE were established, depending on the burdened familial history.

CONCLUSION

The data, obtained in the process of the research, will make it possible to form risk groups of PE at the preclinical stage, and to carry out effective preventive measures in these groups. On the other hand, it will allow to predict the nature of the clinical course of disease among patients, that will optimize the therapeutic-diagnostic process for each patient.
REFERENCES


